Review Article

Perioperative Management of a Patient with Autism

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Abstract

Autism is the fastest growing serious developmental disability in the US. Infantile autism is associated with a characteristic cognitive, language and behavioral features. Autism spectrum disorders (ASD) have lifelong effects on areas of individual daily life functioning such as learning, relationships and independence. We reviewed literature on etiology and causative factors for ASD, and the perioperative management of the disease. In addition, we compared different interventions to make anesthesia induction quicker and smoother, thereby making it a very pleasant experience for the patient and family. The future of anesthetic management of ASD will depend on how well we understand the etiology, psycho-social and medical issues with the disease, thoughtful use of current and newer anesthetic agents (i.e. dexmedetomidine), active involvement of family through the perioperative period, and the availability of a pediatric anesthesiologist.

Introduction

With the May 2013 publication of the DSM-5 diagnostic manual, autism disorders were merged into one umbrella diagnosis of ASD. Previously they were recognized as distinct subtypes including autistic disorder, childhood disintegrative disorder, pervasive developmental disorder- not otherwise specified (PDD-NOS) and asperger syndrome. Autism was first identified in 1943, and is usually diagnosed in early childhood (2-6 years of age) [1]. The signature characteristics of autism are atypical development of behavioral and social skills, and the inability to communicate. Symptoms of autism include, but are not limited to poor social relationships, underdeveloped communication skills, repetitive behaviors, unusual interests and activities, variable degree of intellectual disability, avoiding eye contact, avoiding social contact (preference toward being alone), not understanding other people's feelings and needs, physical aggressiveness, self destructive behavior, and tantrums when provoked [2].

Although this is an evolving field, Research evidence on the effectiveness of intervention for ASDs has shown promise. There are useful interventions that produce positive outcomes for people with ASD [3,4]. Early interventions in the form of intensive behavioral therapy are strongly recommended in the toddler age group since research shows significant improvement in cognitive and language skills [5,6]. It has been suggested that early decline of eye contact at age of 2-6 months can be of value in suspecting the diagnosis. Other suggested guidelines for screening include hearing and vision screen, allergy testing, immune workup, lead levels (if there is history of pica or excessive mouthing), gastrointestinal dysfunction, brain MRI and brain neuro imaging.

The different types of treatments available are generally broken down into the categories of behavior and communication approach, dietary approach, medications, and complementary or alternative medicine. Families of children with ASD have increasingly turned to complementary and alternative medicine (CAM)-that is medicine focusing on traditional forms of medicine which are often non-western [7]. CAM involves diagnosis, treatment, prevention, philosophy and techniques, which can be used in conjunction (complementary) or in place (alternative) of conventional medicine [8]. Many biological based CAM are available for patients with ASD. A diet free of gluten and casein is thought to improve the severity of autism in children since these peptides are hypothesized to impede central nervous system development [9]. On the other hand some other studies have shown a lack evidence to support the effectiveness of a casein and gluten free diet in children with autism [8,10]. Hyperbaric oxygen treatment (HBOT) was also thought to decrease cerebral oxidative stress and neuro inflammation and thus improve symptoms of ASD [11]. One study by Rossignol et al. showed in double-blind placebo controlled study that HBOT improved symptoms in patients with ASD [8]. However, this study has been criticized and a later replication trial by an independent group using similar parameter yielded no significant difference between the placebo and treatment groups in a wide range of social, adaptive and communicative outcomes [12]. HBOT also introduces the potential for serious adverse side effects such as barotrauma and exacerbation of lung disease. Immune therapies [13], such as immunoglobulin treatments for patients with ASD have also been thought to improve symptoms stemming from their possible treatment of central nervous system condition such as multiple sclerosis and guillain Barré [14] similarly; studies have been limited and yielded insufficient evidence to warrant immune therapies for treatment of this population [8]. Acupuncture, another CAM that is gaining popularity in the United States, has had limited studies that were affected by inherent weaknesses; more multicenter double-blind studies of children with autism are needed [14]. We found an article on a drug called Neuro G, a homeopathic medical combination that was found to be effective in about 70% cases of motor or cognitive impairment [15]. The author used it successfully for a variety of conditions including autism, cerebral palsy, Down syndrome, speech or cognitive delays, depression and mood disorders.

At this time the only medications approved by the FDA to treat aspects of ASD are the antipsychotics risperidone (risperidal) and aripripazole (abilify). Risperidone is a novel atypical neuroleptic with favorable profile of side effects due to its unique pharmacological activity: it exhibits both potent dopamine and receptor blocking

activity, as well as high affinity for alpha 1 and alpha 2 adrenergic receptors and histamine 5- HT$_3$ receptor [16]. These medications can help reduce irritability (aggression) and self harming acts (temper tantrums) [17]. Only "typical" antipsychotics have shown replicable chronic ameliorating effects in double blind trials, but with the unwanted side effect of tardive dyskinesia [18]. In animal studies, Risperdone showed significant neuroprotection after permanent focal cerebral ischemia [19]. When epileptiform activity is present in ASDs, therapeutic strategies (antiepileptic drugs, steroids and even neurosurgery) aimed at its control can lead to a significant improvement in language and autistic features [20].

Etiology

Anesthesia is unavoidable for patients with autism, because they need to be sedated for routine procedures, whereas a normal child would cooperate. The incidence of autism and ASD is about 1 in 88 American children, and in public schools 1 in 110 students [21, 22]. Clearly, we must work to minimize the associated risks with anesthesia. To achieve this, the whole team should be involved in the management, and must be made aware of the unique problems that the autistic child may have [2].

The genetic influence is one factor suspected in causing autism, although most people who develop ASD have no reported family history of autism. This would suggest the possibility of random, rare gene mutations which cause the disease. Whole genome sequencing can deliver clear and useful information to families while advancing our understanding of what causes autism. Gene studies of neuro developmental disorders have found an overlap between autism and major mental health conditions [23]. Several postmortem studies have highlighted areas of anatomic abnormality in the autistic brain. Consistent findings have been observed in the limbic system, cerebellum and related inferior olive [24]. At least 10% of children with ASD have an identifiable genetic disorder,-fragile x syndrome. EEG studies are indicated when there is a history of autistic regression, and in those with clinical suspicion of seizures. Commonly associated genetic conditions include Tourette syndrome, fragile x syndrome, phenylketonuria, tuberous sclerosis, and Di George syndrome [25]. Some children may demonstrate delays during the first 18 months of life, while others do well until 18-22 months of age, where they regress into some form of ASD. Researchers have identified several areas of the brain implicated in ASD: the cerebral cortex (frontal lobe), inferior frontal gyrus, superior temporal cortex, parietal cortex, amygdale, hippocampus, caudate nucleus and cerebellum. MRI cross sectional studies of brain volume and head circumference indicates atypical brain growth in the first year of life resulting in enlargement through early childhood. Of course, these cross-sectional findings may not imply accelerated growth and further longitudinal MRI studies are needed to document whether this accelerated growth is normal or abnormal [2]. According to one study, large amygdalar volume on right side when compared with left was associated with more severe clinical course and worst outcome at age six years in children with ASD [26].

The neurochemistry of autism has been extensively studied over the past three decades. Over 25% of children are hyperserotonemic, a familial condition. Also in two other studies, there has been an association between increased plasma norepinephrine and cerebrospinal fluid opiate activity [8]. Multiple theories regarding autism have been proposed, including genetic factors, obstetric conditions, taking medications during pregnancy, environmental factors, and exposure to certain chemicals. According to a recent review, three parental features and two obstetric conditions are identified as true associations: paternal age, maternal age (lesser extent), maternal immigration, newborn hypoxia and growth restriction. After adjusting for cofounders these factors remain significant. To determine if prenatal and perinatal factors are independent risk factors for autism, a measure of genetic susceptibility should be included in future studies [27]. One promising hypothesis is the idea of mitochondrial dysfunction. *Poling* described a case report of an autistic child with mitochondrial dysfunction, growth failure, and abnormal muscle histopathology [28]. An epidemiological survey of 120 children identified 20 % positive for elevated plasma lactate, and of these; 5 children were definitely diagnosed with mitochondrial respiratory chain disorders [29]. This idea has gained interest, and at the American Academy of Neurology 60th annual meeting doctors presented a retrospective analysis of 41 children identifying similar outcomes; 78% of children had defects in skeletal muscle oxidative phosphorylation enzyme function, and 74% had abnormalities within these (OXPHOS) proteins [30].

On the other hand, anesthetics have been a cause of controversy in the pregnant mother as well as newborn child. The most important period of brain growth for the child occurs during the last three months of pregnancy until 2 years after birth. Several animal studies have demonstrated neuro degeneration of subjects, when exposed to anesthetics that block NMDA receptors or hyper activate GABA-A receptors. In one study 6-day-old mice were exposed to a single dose of sevoflurane 3% for six hours and found to exhibit learning deficits and abnormal social behaviors similar to ASD (based on social recognition and interaction tests) [31]. Another study had similar outcomes, where 7-day-old rats were exposed to an anesthesia cocktail of isoflurane, nitrous oxide and midazolam and were found to display some memory and learning deficits [32]. Whether these studies can be applied to humans remains unclear, since each animal species reacts differently when exposed to varying levels of anesthesia. Furthermore, it becomes difficult to directly associate to anesthesia when children are also born preterm and/or have a history of significant peripartum events.

In summary it is difficult to pinpoint one cause for development of autism, but with advancement of technology we have been able to demonstrate certain patterns exhibited in the brains of these individuals. Unfortunately, no definitive links have been identified. There have been patterns of autism and/or related conditions supporting a genetic connection, but researchers have been unable to find any responsible gene. More studies with larger sample sizes and postmortem brain tissue will be instrumental in making further advances.

Perioperative Management

Autistic children are considered difficult patients due to increased anxiety of patient and family members, uncooperative or combative behavior, or in extreme cases very violent behavior of patients. It is critical for the anesthesiologist to recognize these difficult cases and prepare for the necessary interventions beforehand. Following

identification, there must be appropriate pre-anesthetic consultation and careful planning [33], which should include discussion with parents of the anesthetic plan and options. Experienced nursing staff is often invaluable as they are trained in functional communication, and have expertise in managing challenging patients [34]. It is helpful to place autistic children first on the operating list, to minimize the effects of waiting and starvation. A preoperative visit is critical in these children so the anesthesiologist can sit down with the family and formulate a plan. Children are more likely to resist anesthesia when they have a previous history of resisting anesthesia, or have a history of resisting other therapeutic interventions such as immunizations and office visits [35].

Following the recognition of difficult children, an anesthesiologist can introduce various interventions such as: basic explanations/teaching, a visit to the operating room, play therapy, mock anesthesia induction, rewards, and premedication. Various forms of distractions can also be used including music, television, video games, DVDs, toys, lucky dip baskets, and hypnotherapy [36]. Distress during the induction is also associated with younger patient age, preoperative behavior based on assessment, premedication, and venue for anesthesia [37]. Skilled nursing staff, trained specifically in distraction techniques would be useful. Even with careful preoperative planning things may go wrong. In extreme cases kids may become violent or self destructive, refusing all premedication or surgery itself. Physical restraints have been described in literature and although a topic of debate, may be justified in severe cases. When used by trained staff in a decisive, quick and effective manner, they will help to minimize harm to the child and staff [36,38].

Although various nonpharmacologic measures are available to make pre-induction period smooth, they are often not sufficient and premedication becomes a vital part of the pre-induction period. Premedication can modify behavior by providing amnesia, anxiolysis and sedation improving overall compliance. When administered, premedication should be safe and effective and oral route is preferred [34,39]. Oral midazolam is the preferred drug in the US and Europe due to its rapid onset, short duration of onset, and lack of major side effects [40] with a routine dose of about 0.5 mg/kg. Midazolam can be associated with adverse psychotropic effects including disinhibition and at higher doses can cause dysphoria [36,41]. Ketamine can also be used for its sedative and analgesic properties [42]. Oral ketamine in the dose of 8 mg/kg has shown to be more effective in improving compliance during induction of anesthesia. When compared with oral midazolam, benefits of ketamine include less respiratory depression. Ketamine does cause nystagmus, increased salivation, hallucinations and emergence delirium [34,43]. When used alone as a premedicant it has not been found to be effective [40]. Between oral ketamine and oral midazolam there is no significant difference in the postoperative recovery or hospital discharge [43].Oral midazolam is considered to be effective for milder cases of autism, while oral ketamine is preferred in moderate to severe cases. The combination of both drugs may be preferred as they improve compliance with minimal side effects [34,36,44,45]. The use of alpha-adrenergic agonist drugs has been described in literature with a lot of success. Use of clonidine orally in the dose range of 2-4 mcg/kg has been shown to be sedative and anxiolytic in children with ASD [34,46].

Dexmedetomidine first introduced in 1990, is another drug that has gained popularity with more than 1100 published reports on its use. It has shown some promising results in the area of preoperative sedation due to its selective alpha-2 agonist properties [47]. Dexmedetomidine is a particularly attractive premedication because it is both a reliable sedative, and it possesses an excellent safety profile with minimal respiratory depression and hemodynamic changes that are rarely clinically significant [48]. Oral dexmedetomidine has been found to be effective prior to anesthesia induction or procedural sedation even in patients with neurobehavioral disorders in whom previous attempts at sedation have failed [49]. However, it has been shown to significantly depress sinus and atrioventricular nodal function in children, and may not be appropriate for patients with inherent bradycardia or atrioventricular block [50]. Dexmedetomidine can also be used intranasally, though it is difficult to determine an end point due to lack of pharmacokinetic information available. Though optimum dose of intranasal dexmedetomidine for preoperative sedation is not known, higher dosages in the range of 2 mcg/kg have not shown any untoward side effects [51]. Safety profiles of intranasal dexmedetomidine and oral ketamine administration may permit procedures without intravenous cannulation in special circumstances.

The other newer agent remifentanil has gained the confidence of anesthesiologists and has given a real opportunity to change the way anesthesia is given. However its unique pharmacokinetic charactieristics causing rapid onset and offset of effect appear unchanged in small children and even in premature neonates and need to be really confirmed by further pharmacokinetic studies. Also the real risk of tolerance and hyperalgesia needs further evaluation in pediatric population [52,53].

Conclusion

Autism costs a family about $60,000 per year on average, but receives less than 5% of research funding. Increased recognition, the broadening of diagnostic concept over time and methodological differences across studies account for apparent increase in prevalence of ASDs. The possibility that autism has been over diagnosed in recent studies needs to be ruled out. Notwithstanding these important questions, it appears likely that the true prevalence of ASD is considerably greater than previously recognized [54]. There have been number of publications with the key words of autism and communication or language and many of them centered on modes of treatment to improve communication in ASDs. And therefore the natural history of the development of language and nonverbal communication in children with autism has become much more understood [55]. And studies also have shown that video modeling interventions are effective in teaching a variety of skills to children with autism [56,57,58].

We would like to conclude our review by saying that children suffering from ASD have individualized needs and so it is very important to have it planned well in advance [59]. It would be prudent to gain the confidence of child with or without use of premedication. "Hospital passport scheme" [60] is a good example of readiness for care and treatment of children suffering from ASD and associated problems. Properly funded and expertly designed research will enable healthcare professionals to understand more clearly what can and cannot be done for children suffering with ASD [61].

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